REMARKS/ARGUMENTS

In response to the Advisory Action mailed April 14, 2009, Applicant amends his application and requests reconsideration. Claims 1-25 were originally pending in this application. Claims 1-10 and 18-25 are cancelled, however Applicant reserves the right to present the claimed subject matter in a divisional application. Claims 11-17 are pending and undergoing examination. Claims 26 and 27 are new.

Applicant acknowledges that the Examiner has entered the Reply dated April 6, 2009. The Examiner has withdrawn his objections to claims 13-15 in view of Applicant's amendments. The Examiner has also withdrawn the rejection of claims 11-17 under §112, second paragraph, in view of Applicant's entry of a Sequence listing for the tetrapeptide RGDS and referral to SEQ ID NO: 1 in the claims.

Claims 11 and 13-15 have been amended to further clarify and refine that which Applicant considers to be the invention. Applicant has amended the claims to include the feature that the biopolymer support is in the shape of a cornea, having a convex and a concave side. Support for these amendments can be found in the specification, for example, at page 14, paragraphs [0026-0027].

In addition, claims 11 and 13-15 were amended to delete the term "heparin sulfate" from the attachment factors. These amendments are fully supported in the specification as filed, including [0025].

Further, claims 11 and 13-15 were amended to delete the term "comprising" and insert the phrase "consisting essentially of" to further clarify that Applicant's claimed invention does not include other cell types from the cornea. No new matter has been added by these amendments.

Claim 17 was amended to clarify that which Applicant considered to be the invention. Applicant deleted the term "artificial cornea" and inserted "artificial corneal transplant support".

Applicant has added claims 26 and 27 directed to embodiments where the biopolymer of the claimed invention is coated with diamond like carbon. Support for

these claims can be found in Applicant's specification in Examples 9 and 10, pages 30-33.

Discussion of the Novelty Rejection

The Examiner maintained the rejection claims 11-13 and 17 under 35 U.S.C. §102(b), as anticipated by USP 5,827,641 to Parenteau et al. According to the Examiner, Parenteau et al. allegedly teach an artificial corneal transplant support and transplant, comprising a biopolymer with attachment factors, is in the shape of a cornea, and has an inner endothelial layer. Applicant respectfully traverses this rejection.

As previously stated, Parenteau et al. teaches an *in-vitro* corneal model, and does not teach a corneal transplant support comprising a corneal shaped biopolymer having a concave and convex side, and having certain growth and attachment factors incorporated in the polymer. While the abstract of Parenteau et al. and the specification at col. 9, line 66, to col. 10, line 23, speculate that the artificial corneal construct could be used for *in vivo* transplantation, Parenteau et al. is clearly not enabled for this under 35 U.S.C. §112. One of ordinary skill in the art would recognize that the embodiments taught in Parenteau et al. are all *in vitro* models, and there exists no teaching or examples of surgical implantation of such an *in vivo* construct. Parenteau et al. expressly teach that the embodiments of the artificial cornea are not transparent *in vitro*, a property which is necessary in an *in vivo* embodiment, but guesses that it should work:

> *Although not transparent in vitro*, it is expected that the endothelial cells provided by the construct will regulate fluid transport to the corneal stroma and further stimulate the stromal fibroblasts to continue to organize the matrix and produce the appropriate collagens and glycosaminoglycans necessary for corneal clarity. (Parenteau et al., col. 10, lines 13-18, emphasis added)

A reference itself must have an enabling disclosure to be used as a proper reference under §102(b), *Ex Parte Gould*, 231 USPQ 943 (BPAI 1986). The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003). Here, in Parenteau et al., there is no enabling disclosure that teaches that the *in vitro* model disclosed is capable of being transplanted into a living cornea. Moreover, there is no teaching in Parenteau et al. that the endothelial cell layer of the invention, *by itself*, is capable of any function, including transplantation. Thus, Parenteau et al. is not a proper reference for this feature under §102(b).

Furthermore, the *in vitro* model of Parenteau et al. is a completely different construct than Applicant's claimed invention. The Examiner is invited to review cols 5-7 and FIG. 11 of Parenteau et al. which clearly discloses that their model is constructed by placing corneal endothelial cells on top of a cell culture insert, which includes a porous membrane which can have collagen. Next, the endothelial cells are covered with a keratocyte-collagen mixture of cells after culturing separately. Finally, the two layers are covered with a corneal epithelial cell layer.

Nowhere does Parenteau et al. teach Applicant's claimed invention of a corneal shaped biopolymer with a concave and convex side, having growth factors incorporated within the polymer, and having the capability of growing corneal endothelial cells on the concave side which can be transplanted into a cornea surgically, without any other cell types or layers. The cells in Parenteau et al. are grown in a culture well, and as such can expected to be flat or in the shape of a disk, not the shape of a cornea. It is clear from Applicant's specification, that Applicant is not using a flat surface to grow corneal endothelial cells on. Applicant makes multiple references to the concave side of the biopolymer surface (e.g. [0054]) in the specification to this. Parenteau et al., on the other hand, does not teach or claim a composition with a corneal shape with a concave and convex side, where endothelial cells are capable of being placed on the concave side.

In addition, Applicant is claiming a half or full thickness transplant support, where the composition comprises a corneal shaped biopolymer, where the biopolymer component is making up the remainder of the thickness of the composition claimed.

In an embodiment, the corneal endothelial cells are layered on the concave side of the biopolymer. Applicant is not claiming an artificial cornea. There are no stromal cells or epithelial cells in Applicant's claimed invention which is considered to make up the thickness of the cornea as the Examiner suggests. Thus, Parenteau et al. do not teach Applicant's claimed transplant support.

Furthermore, in the rejection, the Examiner maintains that Parenteau et al., teaches endothelial cells grown on collagen and "coated with heparin (i.e. heparin sulfate) and heparin binding growth factor (i.e. bFGF or EGF conjugated with polycarbophil)"(Office Action of 1/7/09 at page 6). Applicant disagrees.

Applicant has carefully reviewed the cited passages of Parenteau et al., col. 5-7, specifically col. 5, lines 21-60 and col. 6, lines 50-65, and could find only a reference to heparin and heparin binding growth factor in conjunction with MSBM medium at col. 6, lines 6-15. Applicant has amended the claims to delete reference to heparin as one of the growth factors incorporated within Applicant's claimed biopolymer. It is unclear to Applicant why the Examiner has included reference to heparin binding growth factor, which is also not included in Applicant's claimed biopolymer. Heparin binding growth factor-1, also known as acidic fibroblast growth factor, is not the same as bFGF (also known as basic fibroblast growth factor, or heparin binding growth factor-2) or EGF. See, for example Kan et al., PNAS (USA) 86:7432-7436 (1989) which discusses how heparin binding growth factor differs from EGF and other growth factors (Attachment A).

The collagen biopolymer layer of the artificial cornea taught in Parenteau et al. does not contain within it, any of the growth factors such as laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, EGF conjugated with polycarbophil as now claimed by Applicant. As such, Parenteau et al. do not teach each and every element of Applicant's amended claims, they cannot be anticipated under 35 U.S.C. §102(b). As such, Applicant respectfully requests withdrawal of the rejection.

Discussion of the Obviousness Rejection

The Examiner also maintained the rejection of claims 11-17 under 35 U.S.C. §103(a), as unpatentable, over Parenteau et al., in view of USP 6,645,715 to Griffith et al., and USP 6,689,165 to Jacob et al. According to the Examiner, Parenteau et al. fail to teach a half-thickness corneal support as recited in claims 14-16, and also fails to teach any of the attachment factors now claimed by Applicant. Griffith et al. is offered by the Examiner for teaching the attachment factors such as laminin, fibronectin, bFGF and the like. The Examiner offers Jacob et al. for teaching that epithelial cell adhesion is augmented by growth factors on the polymer surface of an artificial corneal construct. The Examiner then concludes that it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the construct of Parenteau et al., with the attachment factors of Griffith et al. Applicant traverses this rejection.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 US 1, 148 USPQ 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art, and (4), objective evidence of nonobviousness. *Graham*, 3838 US at 17-18, 148 USPQ at 467.

Consideration of the aforementioned Graham factors here indicates that the present invention, as defined by the amended claims, is unobvious in view of specification and claims of the present patent application.

With regard to the differences between the cited references and Applicant's invention in view of the amended claims, Applicant submits that none of these references teaches a biopolymer in the shape of a cornea, having a concave and

convex side, and having growth and attachment factors incorporated *within* the biopolymer, that is suitable for transplantation into a damaged cornea, as now claimed by Applicant. Parenteau et al. was discussed above. As stated previously, Griffith et al. teach an *in-vitro*, avascular, human corneal equivalent, comprising immortalized human cell lines, not a corneal biopolymer support suitable for transplant into a cornea (abstract, col.7 – col. 8). All the teachings or examples in Griffith et al., where a biopolymer support suitable for long term growth of human corneal endothelial cells is produced, use only immortalized cells which cannot be transplanted. The growth factors mentioned in Griffith et al. are in the media, and used to test the cell lines, not incorporated in the biopolymer support as claimed by Applicants (Griffith et al., at col. 7). The Examiner points to col. 15-16 for teaching that human corneal cells can be used in the corneal transplant. Applicant asserts that the Examiner has mischaracterized the teaching of Griffith et al.

Close reading of Griffith et al. reveals that Griffith et al. is teaching whole organ culture medium, and the use of cadaverous whole human corneas in organ culture, not Applicant's claimed preparation of a synthetic corneal endothelial transplant support and transplant consisting essentially of a biopolymer in the shape of a cornea, having a concave and convex side, and having growth and attachment factors incorporated *within* the biopolymer, that is suitable for transplantation into a damaged cornea. The whole cornea organ culture of Griffith et al. is not suitable for transplantation, it is used to test wound healing in vitro (Griffith et al. at col. 17).

As stated previously, Jacob et al. teach an ocular device comprising an optical polymer having biocompatible linear, single chain tether molecules having two ends, attached to the optical polymer on one end of the tether, and a corneal enhancer molecule or growth factor attached to the tether at the other end. As Applicant discussed previously, the device of Jacob et al. is designed for growth of corneal epithelial, cells, on the convex or outside surface of the device. In contrast, Applicant's invention is directed to an artificial stroma for growth of corneal endothelial cells on the concave or inside surface of the cornea. The cell type taught in Jacob et al. is completely different than the cell type used by Applicant. Jacob et al. also teach that the corneal enhancer molecules or growth factors must be tethered or otherwise covalently bound to the optical polymer via a linear polyethylene oxide

(PEO) molecule, or amino acid or peptide, with a molecular weight between 2000-8000. Applicant's claimed support does not use any such chemical modifications.

For purposes of the present analysis, Applicants consider that the level of ordinary skill in the art can be considered to be reasonably high, such that a person of ordinary skill in the relevant art would have an advanced degree in chemistry and/or chemical engineering, as well as several years of experience in the relevant field of ophthalmology.

Considering all of the Graham factors together, it is clear that the Applicant's invention, as now presently claimed, would not have been obvious to one of ordinary skill in the art, at the relevant time, in view of the prior art references. Applicant submits that the combination of teachings of Parenteau et al., in view of Griffith et al. and Jacob et al., do not teach each and every feature of Applicant's claimed invention. Furthermore, a rationale to support a conclusion that a claim would have been obvious requires that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 US 398, 408, 82 USPQ2d 1385, 1395 (2007).

The Court in *KSR* noted that obviousness cannot be proven merely by showing the elements of a claimed device were known in the art; it must be shown that those of ordinary skill in the art would have had some "apparent reason" to combine the known elements in the fashion claimed. *KSR* at 1741. In the same way, when the prior art teaches away from the claimed invention, as shown in Appellant's arguments and other objective evidence, obviousness cannot be proven by merely showing that the biopolymer composition and growth factors were known, and corneal endothelial cells could be modified by routine experimentation. See, *Ex parte Whalen* II, Appeal 2007-4423, (BPAI July 23, 2008) at pp. 13-16.

Applicant submits that one of ordinary skill in the art, in an attempt to improve corneal endothelial grafts, one would not have looked to Parenteau et al., in view of Griffith et al. and Jacob et al., because Parenteau et al. and Griffith et al. do not teach anything about implantable corneal constructs. Moreover, both Parenteau et al. and

Griffith et al. teach entire corneal constructs including stroma and epithelial cells, not Applicant's biopolymer support and endothelial cells. The methods and reagents used to grow the different cell types are not applicable in Applicant's claimed invention.

Further, one of ordinary skill in the art would understand that Griffith et al. teach that only transformed endothelial cells are able to maintain sustained growth in culture, and that Jacob et al. teach that the growth factors must be covalently bound to the optical polymer (not incorporated within it) to allow cell growth, and teaches the use of epithelial cells on outer or convex surface of the cornea, not the use of endothelial cells on the inner, or concave surface as Applicant claims. In Applicant's invention, the combination of attachment factors do not have to be covalently bound, but only mixed into the polymer, to be effective. Applicant's claimed method is simpler, and more effective and less costly, as there are no synthesis steps for making the tethered growth factors.

Applicant submits that the combination of Parenteau et al., in view of Griffith et al. and Jacob et al. does not make Applicant's claimed invention *prima facie* obvious, because: 1) the combination of references does not teach each and every element of Applicant's claimed invention, namely, the combination of references does not teach both the use of only non-transformed human corneal endothelial cells, and the use of a biopolymer having growth factors incorporated into it and shaped as a cornea, which is suitable for transplantation; and 2) the combination of references teaches away from Applicant's invention, because the primary reference of Parenteau et al. and Griffith et al. are directed to immortalized human corneal endothelial cells (not cells from a patient's cornea), which could never be ethically implanted into a patient for fear of cancer, and the secondary reference of Jacob et al. teaches away from Applicant's claimed invention, because it teaches that growth factors must be covalently bound or teathered to the biopolymer to work, and is directed to a completely different corneal cell type.

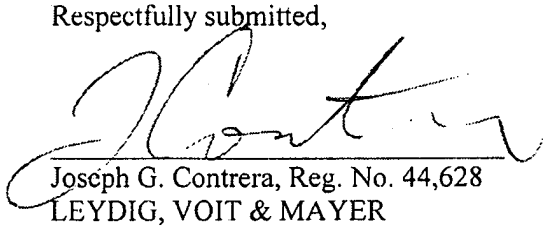
Again, the Examiner's reliance on *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981) is misplaced. Applicant has not attacked the references individually. Applicant has discussed the teachings of each cited reference, and then has shown that when the *combination of references* is considered, the *combination* of teachings

cannot render Applicant's claimed invention, *as a whole*, *prima facie* obvious, because the combination of teachings do not encompass all of Applicant's claimed features, and because the combination of teachings teach away from Applicant's claimed invention. As such, Applicant respectfully requests withdrawal of this rejection.

Conclusion

Applicant respectfully submits that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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ATTACHMENT A